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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
BELYAVSKYI, MICHAIL A	
ART UNIT	PAPER NUMBER
1644	

DATE MAILED: 04/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/988,127	PELED ET AL.	
	Examiner	Art Unit	
	Michail A Belyavskyi	1644	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *10 February 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37,43 and 101-105* is/are pending in the application.

4a) Of the above claim(s) *104 and 105* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37,43 and 101-103* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

RESPONSE TO APPLICANT'S AMENDMENT

1. Applicant's amendment, filed 02/10/2004 is acknowledged.

Claims 37, 43 and 101-105 are pending.

Newly submitted claims 104 and 105 directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The elected Group I, claims 37-43, now claims 37, 43 and 101-103 drawn to a method of in vivo expanding a population of cell, while at the same time inhibiting differentiation of said cells. Newly submitted claims 104 and 105 drawn to a method of mobilizing hematopoietic stem cells in a peripheral blood cell donor.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 104 and 105 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

Claims 37, 43 and 101-103, as they all read on a method of in vivo expanding a population of hematopoietic cell , while at the same time inhibiting differentiation of said cells comprising administrating an effective amount of a transition metal chelator having affinity for copper wherein , tetraethylenepentamine (TEPA) is specific transition metal chelator, are under consideration in the instant application.

In view of the amendment, filed 02/10/2004 and declaration of Dr. Eitan Fibach under 37 CRF 1.132 the following rejection remains

2. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 37, 43 and 101-103 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of *ex-vivo* expanding a population of hematopoietic cells while at the same time inhibiting differentiation of said cells, the method comprising a step of providing hematopoietic cells *ex-vivo* with conditions for cell proliferation

and at the same time for reducing a capacity of said cells in utilizing copper, does not reasonably provide **enablement** for: (i) a method of *in vivo* expanding a population of hematopoietic cells while at the same time inhibiting differentiation of the hematopoietic cells, the method comprising the step of administering to a patient in need thereof an effective amount of a transition metal chelator having affinity for copper, as claimed in claim 37 , or (ii) a method of expanding a population of hematopoietic cells while at the same time inhibiting differentiation of the hematopoietic cells, the method comprising the step of administering to a patient in need thereof an effective amount of a transition metal chelator having affinity for copper, wherein said patient has hemoglobinopathy or wherein said hemoglobinopathy is sickle cell anemia or β thalassemia, as claimed in claimed 101-103 . The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and or use the invention commensurate in scope with this claim for the same reason set forth in the previous Office Action, mailed on 08/11/03.

Applicant's arguments, filed 02/10/2004 have been fully considered, but have not been found convincing

Applicant asserts that: (i) the claimed in vivo methods are supported by the teaching and examples provided in the specification relating to the in vitro effects of transition metal chelators on hematopoietic cells; (ii) Declaration of Dr. Eitan Fibach provides additional evidence that non-CD34+ selected cells proliferate without differentiating; (iii) Enablement rejection is improper under MPEP paragraph 2107.03, which states that it is improper to request evidence of safety in the treatment in humans; (iv) transition metal chelators have been used *in vivo* to treat various conditions as evidence by the provided literature.

Contrary to Applicant's assertion it is the Examiner position that the specification does not adequately teach the effectively of a method of expanding *in vivo* a population of hematopoietic cells while at the same time inhibiting differentiation of the hematopoietic cells, comprising the step of administering to a patient in need thereof an effective amount of a transition metal chelator having affinity for copper, as claimed in claim 37 , or (ii) a method of expanding a population of hematopoietic cells while at the same time inhibiting differentiation of the hematopoietic cells, the method comprising the step of administering to a patient in need thereof an effective amount of a transition metal chelator having affinity for copper, wherein said patient has hemoglobinopathy or wherein said hemoglobinopathy is sickle cell anemia or β thalassemia, as claimed in claimed 101-103. The specification does not teach how to extrapolate data obtained from $CD4^+$ cells *ex-vivo* assay studies to the development of effective *in vivo* protocols for imposing proliferation and at the same time restricting differentiation of hematopoietic cells by providing said cells with conditions that reduces the capacity of said cells in utilizing copper. In addition, no animals were used as model system to effectively expand hematopoietic cells *in vivo* by providing said cells with conditions for cell proliferation and at the same time for reducing a capacity of said cells in utilizing copper or expand a population of hematopoietic cells while at the same time inhibit differentiation of the hematopoietic cells, the method comprising the step of administering to a patient in need thereof an effective amount of a transition metal chelator having affinity for copper, wherein said patient

has hemoglobinopathy or wherein said hemoglobinopathy is sickle cell anemia or β thalassemia. Since there is no animal model data in the specification to teach the effectively of a method of expanding *in vivo* a population of hematopoietic cells while at the same time inhibiting differentiation of the hematopoietic cells, comprising the step of administering to a patient in need thereof an effective amount of a transition metal chelator having affinity for copper, as claimed in claim 37 , or (ii) a method of expanding a population of hematopoietic cells while at the same time inhibiting differentiation of the hematopoietic cells, the method comprising the step of administering to a patient in need thereof an effective amount of a transition metal chelator having affinity for copper, wherein said patient has hemoglobinopathy or wherein said hemoglobinopathy is sickle cell anemia or β thalassemia, as claimed in claimed 101-103it is unpredictable how to correlate *in vitro* results with *in vivo* use. Thus in the absence of working *in vivo* examples or detailed guidance in the specification, the intended uses of a method of *in-vivo* expanding a population of hematopoietic cells while at the same time inhibiting differentiation of said cells, the method comprising a step of providing cells with conditions for cell proliferation and at the same time for reducing a capacity of said cells in utilizing copper are fraught with uncertainties. Moreover, in Applicant's Declaration under 37 CFR 1.132, Dr. Eitan Fibach clearly stated that the specification disclosed method for only *ex vivo* expansion of and inhibition of hematopoietic cells; and for successful *ex-vivo* expansion both the number of the cells recovered following the enrichment procedure and the purity of the progenitor cell fraction are two crucial parameters. (see Declaration of Dr. Eitan Fibach, pages 2 and 5 in particular). In addition, Applicant himself acknowledge that the mechanism of the effects of cupper is unknown (see page 3, line 35-37 in particular). As such, the invention must be considered unpredictable. In addition, Percival (Am .J. Clin. Nutr. 1998, Vol.67 p.1064-1068) teaches that the role of copper in effecting cellular function is contradictory and that more studies have to be done to understand the mechanisms by which copper effect the process of differentiation in various types of cells (see entire document, pages 1064 and 1066 in particular).

With regards to the issues of improper rejection under MPEP paragraph 2107.03 and *in vivo* use of transition metal chelators to treat various conditions.

It is noted that MPEP paragraph 2107.03 addressed utility rejection under 35 U.S.C. 101, not enablement rejection under 35 U.S.C. 112 first paragraph. In the instant case, the enablement rejection was made under 35 U.S.C. 112 first paragraph. Moreover, in the previous Office Action there was no request for the evidence of safety in treatment in humans, but rather a need to show that the invention will work as claimed. In the absence of working *in vivo* examples the *in vivo* use of a transition metal chelator which binds copper such as ethylendiamine or tetraethylenepentamine (TEPA) is considered potential health hazard because according to ChemMaster Safety Data Sheet (1999, pages 1-4) and The Merk Index (1983, Tenth edition, page 3742) ethylendiamine or tetraethylenepentamine (TEPA) are helth hazards and care must be taken in handling because of the caustic nature of ethylendiamine or tetraethylenepentamine (TEPA) and since it may cause allegic respiratory reaction, headaches, nausea and dizzness. The referenced provided by the applicant only disclosed *in vivo* use of a well known copper chelating agents 2,3 dimercaptopropanol and d-penicillamine (see exhibits A and B, D and E in

particular). However, it is noted that none of the provided references teaches the *in vivo* use of the claimed transition metal chelators such as ethylendiamine or TEPA. Moreover, neither 2, 3 dimercaptopropanol no d-penicillamine is recited in any of the pending claims as a transition metal chelator to be used in a method of expanding a population of hematopoietic cells *in vivo.*

Thus, Applicant has not provided sufficient guidance to enable one skill in the art to use : (i) a method of *in vivo* expanding a population of hematopoietic cells while at the same time inhibiting differentiation of the hematopoietic cells, the method comprising the step of administering to a patient in need thereof an effective amount of a transition metal chelator having affinity for copper, as claimed in claim 37 , or (ii) a method of expanding a population of hematopoietic cells while at the same time inhibiting differentiation of the hematopoietic cells, the method comprising the step of administering to a patient in need thereof an effective amount of a transition metal chelator having affinity for copper, wherein said patient has hemoglobinopathy or wherein said hemoglobinopathy is sickle cell anemia or β thalassemia, as claimed in claimed 101-103 in manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement. *In re Fisher*, 166 USPQ 18(CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute.

In view of the quantity of experimentation necessary, the unpredictability of the art, the lack of sufficient guidance in the specification, the limited working examples, and the limited amount of direction provided given the breadth of the claims, it would take undue trials and errors to practice the claimed invention.

The following new ground of rejections are necessitated by the amendment filed 02/10/2004

3. The following is a quotation of the second paragraph of 35 U.S.C. 112.

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

4. Claim101 - 103 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A) Claim 101 recites "said individual" There is insufficient antecedent basis for this limitation in the claim since the base claim 37 does not recites "individual".

B) Claim 102 is indefinite and ambiguous in being dependent upon itself.

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 101-103 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a New Matter rejection**.

" .. wherein said individual has a hemaglobinopathy" claimed in claim 101 represent a departure from the specification and the claims as originally filed. The passages pointed by the applicant do not provide a clear support for the general term "hemaglobinopathy". The specification as originally field only support " β–hemaglobinopathy".

7. No claim is allowed.

8. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michail Belyavskyi whose telephone number is 571/ 272-0840 The examiner can normally be reached Monday through Friday from 9:00 AM to 5:30 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on 571/ 272-0841 .

The fax number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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